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Applicants: Matthieu Guitton *et al.*	Confirmation No.: 1803
Serial No.: 10/812,298	Examiner: Jennifer Kim
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For: **METHODS FOR THE TREATMENT OF TINNITUS INDUCED BY COCHLEAR EXCITOTOXICITY**	Attorney Docket No.: 067802-3000-001

DECLARATION UNDER 37 CFR §1.132

Dear Sir:

I, Richard J. Salvi, Ph.D., declare and state as follows:

1. I am employed as Professor, University at Buffalo; Dept. Communicative Disorders and Sciences 1987-present; Clinical Professor of Otolaryngology, University at Buffalo, Dept. of Otolaryngology; Clinical Assistant Professor, University at Buffalo, Dept. of Neurology, 1997-present; Clinical Professor, Univ. of Rochester, Dept. of Otolaryngology, 1997-present;

- I received my Ph.D. in Experimental Psychology from Syracuse University in 1975.
- I received my B.S. in Psychology from North Dakota State University in 1968.

2. I am a member or past member of the following scientific societies and associations pertaining to audiology, communications and acoustics:

- Acoustical Society of America (past member)
- American Association for the Advancement of Science
- American Auditory Society (past member)
- American Speech, Language and Hearing Association
- Association for Research in Otolaryngology
- Committee on Hearing, Bioacoustics and Biomechanics (CHABA) (past member)
- Society for Neuroscience

- The International Society of Complex Environmental Studies, (Member of the Board of Directors) (past member)
- Chair, Scientific Advisory Board, American Tinnitus Association (2001-2008)
- Board of Directors, American Tinnitus Association (2001-2008)
- Tinnitus Research Initiative, Scientific Committee, 2007-present
- Chair, Scientific Committee, Tinnitus Research Initiative, July 2009-present.

I am on the Editorial Board of the following scientific journals:

- Hearing Research, 1993-present
- Audiology and Neuro-Otology, 1995-present
- International Tinnitus Journal, 1997-present
- Noise & Health, 1998-present
- Chinese Journal of Otolaryngology, editorial board
- American Academy of Audiology 1999-present
- Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine, 2001-present
- Journal of Audiological Medicine and Sciences Related to Communicative Disorders, 2004-present
- Chinese Journal of Otolaryngology, 2003-present
- Iranian Journal of Audiology, 2002-present
- Open Otorhinolaryngology 2007-present
- Guest Editor, Seminar in Hearing; Advances in Tinnitus (2007-2008)

I have published over 300 scientific articles in the fields of audiology, communications and acoustics. (A listing of the articles is available upon request).

3. I have hitherto participated in a scientific collaboration on tinnitus with representatives of the Assignee of the presently pending U.S. Patent Application Number 10/812,298 (Auris Medical AG). However, I have no inventive or financial interest in the presently pending U.S. Patent Application Number 10/812,298.

4. Prior to making this Declaration I studied the following documents:

- U.S. Application Number 10/812,298 (herein after "the '298 application");
- The technical article by Tabuchi, et al., Ann. Otol. Rhinol. Laryngol., (2002) Vol. 111, pp 44-49 (hereinafter "Tabuchi");
- The US Patent to Donovan (U.S. Patent No. 6,265,379, issued July 24, 2001; herein after "Donovan"); and

- The Office Action dated April 1, 2009 with respect to the technical aspects of the remarks as presented by the Examiner in regard to the Tabuchi and Donovan references.

5. I understand all claims pending in the '298 application (Claims 1 and 4-9) have been rejected as "obvious" by the Patent Office because of the combination of technical disclosures found in Tabuchi and Donovan. The obviousness standards have been explained to me by patent counsel.

6. The '298 application currently claims a method for treating tinnitus induced by cochlear excitotoxicity in a human, the method comprising administering to the human a therapeutically effective amount of a pharmaceutical composition comprising the NMDA receptor antagonist ketamine, effective to suppress or reduce NMDA receptor mediated aberrant activity of the auditory nerve in a human in need of such treatment and correlating the administration of ketamine with a reduction in tinnitus. (Claim 1)

7. In making this declaration, I conclude the following:

- Tabuchi and Donovan would not have provided a scientist working in the field in March 2004 with a reasonable expectation that ketamine would have been effective in the treatment of tinnitus as claimed.

- A scientist reading Tabuchi in March 2004, would have been dissuaded from using NMDA receptor antagonists such as ketamine, in the treatment of a disorder associated with excitoxicity in inner hair cell auditory nerve synapses.

- That a scientist working in the field in March 2004 would have been dissuaded from combining Tabuchi and Donovan in attempting to develop the claimed methods of treating tinnitus in the manner suggested by the Examiner.

- That treating tinnitus with ketamine in the manner claimed in the '298 application provides results that meet a long felt and unmet need and which overcome the failure of others to provide suitable treatments for tinnitus in March 2004.

8. "Cochlear dysfunction" is a term that refers to a physiological malfunction within the cochlea or its associated tissues. Cochlear dysfunction may be associated with the cochlea's blood supply, tectorial membrane, inner hair cells, outer hair cells, spiral ganglion neurons, afferent auditory nerve fibers, efferent nerve fibers and many different types of supporting cells in the stria vascularis, spiral ligament, organ of Corti, inner sulcus and/or the osseous bony labyrinth.

9. Cochlear dysfunction can result from a number etiologies including but not limited to congenital birth defects, noise exposure, vascular disruptions, viruses, aging, ototoxic drugs or surgical removal of the auditory nerve.

10. The term "cochlear dysfunction" is an "umbrella" or "catch-all" term for a disturbance in the functioning of the cochlea. A cochlear dysfunction is generally not a diagnostically useful medical term since it fails to specify the exact type of dysfunction or recommend a course of treatment. It cannot be observed directly, but only through its symptoms or in some cases structural imaging of the cochlea. A cochlear dysfunction does not specify the type of symptoms that may or may not arise from it.

11. Symptoms arising from cochlear dysfunction can include but are not limited to hearing loss, poor speech discrimination, impaired auditory temporal resolution and temporal summation, diplacusis, hyperacusis, loudness recruitment, impaired localization and tinnitus.

12. "Tinnitus" is the perception of sound in the absence of any external acoustical stimulation. Tinnitus is not a disease but a symptom resulting from a range of known and unknown underlying causes. In the case of tinnitus originating in the cochlea, onset factors include but are not limited to overexposure to loud sound, presbycusis, reduced cochlear blood flow, Meniere's disease (endocochlear hydrops), infections of the inner ear, barotrauma, allergies, ototoxic medications such as certain antibiotics or chemotherapeutics, antiviral drugs, diuretics, anti-depressants, quinine, or psychedelic drugs.

13. Given the wide range of pathologies and lesions associated with cochlear dysfunction and the wide range of symptoms that could result from it, a person skilled in the art in March 2004 would not have reasonably expected that treatment of one symptom associated with cochlear dysfunction would be effective in the treatment of another.

14. Many compounds were tested prior to March 2004 for their ability to reduce hearing loss. However, none were to my knowledge effective in the treatment of both hearing loss and tinnitus. Caroverine was reported by Chen et al., Acta Otolaryngol. 2003 Oct;123(8):905-9 to decrease hearing impairment after noise trauma when applied 1 but not 24 h after noise exposure. However, initial claims of the potential therapeutic efficacy of caroverine for treatment of tinnitus by Denk et al. (Otolaryngol (Stockh) 1997; 117(6):825-830), could not be confirmed by a later study by Domeisen et al. (Acta Otolaryngol 1998;118(4):606-608). Indeed, planned clinical trials using caroverine to treat tinnitus were abandoned because of inconsistent results (Dobie et al., Laryngoscope. 1999 Aug;109(8):1202-11). Caroverine's ineffectiveness in treating tinnitus was further demonstrated by Schwab et al., who showed that caroverine was unable to ameliorate tinnitus in a significant manner (Laryngorhinootologie. 2004 Mar;83(3):164-72). Schwab et al. also showed that glutamic acid diethyl ester was ineffective at treating tinnitus.

15. Wang et al. J Neurosci. 2003 Sep 17;23(24):8596-607 demonstrated that D-JNKI-1 prevented acoustic trauma-induced permanent hearing loss in a dose-dependent manner. D-JNKI-1 provides strong protection against neuronal death and loss of cochlear hair cells. The experiment described in Paragraph [0062-0064] of the'298 application confirms that D-JNKI-1 enhances recovery of auditory function following acute acoustic trauma. However, the '298 application also describes how D-JNKI-1 similar to untreated control animals, failed to decrease the number of behavioral correlates of tinnitus in an animal model. See Paragraphs [0048] and [0064]. Ketamine on the other hand, blocked a permanent increase in the behavioral correlate of tinnitus.

16. Tabuchi discloses the potential treatment of hearing loss resulting from cochlear dysfunction induced by transient ischemia with the NMDA receptor antagonists: ketamine, dextromethorphan and MK-801. Tabuchi demonstrated that MK-801 did not improve compound action potential ("CAP") threshold shifts following transient ischemia compared to control; whereas ketamine and dextromethorophan were able to moderately improve CAP threshold shifts.

17. The CAP is a physiological measure arising from the synchronous discharge of auditory nerve fibers in response to the onset of a suprathreshold *sound* stimulus. It is commonly used in hearing research for testing the function of cochlear hair cells and the auditory nerve. In contrast, tinnitus is a subjective auditory sensation that occurs in the *absence* of external sound stimulation. The CAP, being a sound evoked electrophysiological potential, cannot be used to make any logical inference about the presence or absence of tinnitus which is a subjective phenomenon that requires a behavioral response from a patient indicating he/she is experiencing a phantom auditory sensation. The protective effects of ketamine on CAP measurements would, therefore, not have taught a scientist in March 2004 anything about the efficacy of using ketamine to treat tinnitus as claimed. As such, the protective effects of ketamine on the CAP measurements would not have provided a scientist of the time with a reasonable expectation that ketamine would be effective in treating tinnitus as claimed. The fact that Tabuchi's experiments were done *in vivo* would not have impacted this conclusion.

18. Reviewing Chen et al., Denk et al., Domeisen et al., Wang et al., Dobie et al., Schwab et al.. and Tabuchi, the person of skill in the art in March 2004 would not have had a reasonable expectation that a therapy potentially effective for the treatment of hearing loss associated with cochlear dysfunction would also be successful in treating tinnitus as claimed.

19. Indeed, a scientist reading Tabuchi in March 2004, would have been dissuaded from using NMDA receptor antagonists such as ketamine, in the treatment of any disorder associated with excitotoxicity involving the inner hair cell auditory nerve synapses.

20. Tabuchi "concluded" that "NMDA-receptor antagonists do not have any protective effect on cochlear ischemia-reperfusion injury." Additionally, Tabuchi stated that, "this result is consistent with the morphological findings observed during ischemia by Pujol et al. and Puel et al." Tabuchi cited Pujol et al., Neuroreport, 1992; 3:299-302 and Puel et al., J. Comp Neurol., 1994;341:241-56 for the proposition that the NMDA receptor antagonist D-AP5 had no protective effect on the ischemia-induced swelling of the radial dendrites. (Tabuchi page 48, left column)

21. According to Tabuchi, ketamine can improve CAP threshold shifts following transient ischemia compared to control. Beyond speculation relating to nitric oxide antagonism and dopamine release up-regulation, Tabuchi fails to provide a specific mechanism by which ketamine improves CAP threshold shifts. (Tabuchi page 48/49 bridging paragraph) Tabuchi is silent as to what effect, if any, ketamine might have on ischemia-induced swelling of the radial dendrites. Tabuchi states that "[i]t is highly likely" that ketamine and dextromethorophan produced their activity, "via pathway(s) other than NMDA-receptor inhibition." (Tabuchi page 48, left column)

22. Whatever ostensibly beneficial "pathway" was exploited by ketamine to partially reduce CAP threshold shifts following transient ischemia, it must be kept in mind that ketamine nevertheless retains its NMDA-receptor antagonism as its primary pharmacological characteristic. Tabuchi states that the NMDA-receptors are "important in repair of the inner hair cell-auditory nerve synapses." (Tabuchi page 48, right column) Tabuchi further states that the NMDA-receptor antagonist D-AP5 was shown to delay recovery from AMPA excitoxicity in inner hair cell auditory nerve synapses. Therefore, even though ketamine might be able to partially reduce CAP threshold shifts through some non-NMDA pathway, ketamine nevertheless remains an NMDA-receptor antagonist which according to Tabuchi is likely to delay recovery from excitoxicity in inner hair cell auditory nerve synapses.

23. This conclusion is further supported by the experimental results described in the '298 application. Paragraph [0063] describes an experiment wherein the NMDA receptor antagonists ketamine and 7-chlorokynurenate ("7-CK") were demonstrated to in fact, delay hearing recovery following acute acoustic trauma compared to untreated animals in a manner consistent with what would have been predicted by Tabuchi. See also Figures 4A and 5A of the '298 application.

24. Given that Tabuchi would have dissuaded a scientist in March 2004, from using an NMDA receptor antagonist such as ketamine in the treatment of a symptom or disorder associated with excitoxicity in inner hair cell auditory nerve synapses; it also teaches away from a combination with Donovan as suggested by the Examiner.

25. Donovan states that a particular form of inner ear tinnitus results from functional disturbances of the synapse between cochlear hair cells and afferent dendrites of the auditory nerve. Donovan also states that the neurotransmitter at the afferent cochlear synapse is glutamate and that patients having such tinnitus receive infusions of the glutamate antagonists, glutamic acid diethyl ester and caroverine. Notwithstanding that a scientist in March 2004 would have been unimpressed by Donovan's erroneous supposition that glutamic acid diethyl ester and caroverine were actually effective at treating tinnitus (see Paragraph 14 above); Donovan implies that there is an excessive release of glutamate at the afferent cochlear synapse. (Donovan at 2:54-62)

26. The two primary glutamate receptors are named after agonists that bind to them with high specificity: AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) and NMDA (N-Methyl-D-Aspartate). Overstimulation of glutamate receptors causes neurodegeneration and neuronal damage through excitotoxicity. Therefore, Donovan implies that too much glutamate at the afferent cochlear synapse results in overstimulation of its glutamate receptors and leads to excitoxicity.

27. However as stated above, Tabuchi specifically states that NMDA antagonists delay recovery from excitoxicity. As such, even if Tabuchi suggested the use of ketamine in tinnitus (which it does not), Donovan would have dissuaded a scientist from trying such a treatment because it implies that the tinnitus is a result of excitoxicity. The aforementioned scientist would not have combined Donovan and Tabuchi in the manner asserted by the Examiner because they would not have wanted to treat the ostensible excitoxicity-associated tinnitus described in Donovan by *delaying* recovery from the excitoxicity with an NMDA receptor antagonist such as ketamine as described in Tabuchi. As such, the scientist would not have felt that the combination would have yielded an appropriate therapy for treating tinnitus as claimed.

28. Not only does Tabuchi teach away from a combination with Donovan; Donovan also teaches away from a combination with Tabuchi. According to Tabuchi, ketamine can improve CAP threshold shifts following transient ischemia compared to control through some non-NMDA pathway. Tabuchi speculates that the non-NMDA pathway might be associated with dopamine release up-regulation. (Tabuchi page 48/49 bridging paragraph) Donovan advocates the use of botulinum toxin ("Botox") in the treatment of tinnitus. However, Donovan states that Botox inhibits the release of dopamine and glutamate. (Donovan at 4:41-49) Therefore, a scientist reading Donovan would have been led to believe that tinnitus treatment should be associated with a reduction in dopamine release. Accordingly, a scientist would not have used an agent such as ketamine – which according Tabuchi might be associated with dopamine release up-regulation – for the treatment of tinnitus as claimed.

29. Tinnitus is very common and its history goes all the way back to the Egyptians. Many patients suffer severely from tinnitus as it can affect everyday activities considerably.

30. Prior to March 2004, many investigators tried and failed to develop suitable pharmacological therapies for the treatment of tinnitus. None of the treatment options available in March of 2004 was able to achieve a lasting effect and therapeutic success.

31. These treatment options ranged from telling patients to "just live with it" to counseling to using certain devices such as hearing aids, tinnitus maskers, and tinnitus instruments. Although these devices could offer some relief, patients suffering from tinnitus also commonly tried acupuncture, ginko biloba, vitamins and hyperbaric oxygen therapy. However, none of these latter options were proven to be effective.

32. Acute tinnitus was occasionally treated with infusions of cortisone or pentoxifylline or a short-term oral medication with these substances. Pentoxifylline was given to adjust cochlear blood flow and cortisone was provided for inner ear inflammation. However, neither of these drugs specifically treats tinnitus nor are they suitable for longer term administration.

33. Other treatment options commonly used in 2004 generally only addressed the psychological impact of tinnitus and not the actual tinnitus symptoms suffered by the patient, e.g., the prescription of the drug alprazolam, also known under the trade name "Xanax." Alprazolam is habit-forming and long-term use and abuse may cause a physical dependence to develop along with withdrawal reactions during abrupt or rapid discontinuation. Other drugs similarly prescribed in 2004 for tinnitus were tricyclic anti-depressants e.g., nortriptyline, or SSRIs like Prozac and Paxil.

34. Donovan suggests that tinnitus might be treated by Botox-mediated denervation or "[a]uditory nerve section." However, not only do these interventions lead to permanent or semi-permanent hearing loss in the treated ear, they result, "often with the condition worsening because the tinnitus was not due to a cochlear disorder." See Donovan at Col. 3:12-16. These were unacceptable risks and side effects for most patients in March 2004.

35. The failure of caroverine (erroneously described as a treatment option by Donovan) to present a suitable treatment option is discussed in Paragraph 14 above.

36. Lidocaine had been reported to produce some improvement in tinnitus. However, by 2004 it had largely been abandoned as a therapy because of its severe side-effect profile and need for inpatient administration as well as unreproducibility of results. Dobie et al., Laryngoscope. 1999 Aug;109(8):1202-11; Dodson et al., Otolaryngol Clin North Am. 2004 Oct;37(5):991-1000. These side-effects included cardiac rhythm disturbances, vertigo, nausea and vomiting. Schwab et al.. Laryngorhinootologie. 2004 Mar;83(3):164-72. Lidocaine can also induce tinnitus. (Reyes

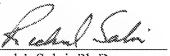
et al., Hear. Res. 171, 43-50). Donovan also mentions the "serious toxicity" of lidocaine. (Donovan at 2:64-65)

37. A search of the FDA's Clinicaltrials.gov database revealed no clinical trials testing new drugs for the "condition" tinnitus prior to January 1, 2004.

38. However, the assignee of the '298 application, Auris Medical, has completed a phase I/II and initiated a phase IIb clinical trial with "AM-101," an investigational ketamine-based drug for the treatment of inner ear tinnitus.

39. In view of the long felt need for effective treatments of tinnitus and the failure of others to identify suitable therapies; the invention of the use ketamine for the treatment of tinnitus as claimed and described in the '298 application represents a significant breakthrough.

40. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Richard J. Salvi, Ph.D.

January 6, 2010

Date